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CONTENTS

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THE USE OF CHLORAMPHENICOL ("CHOROMYCETIN")* IN THE TREATMENT OF INFECTIONS OF THE URINARY TRACT IN CHILDHOOD†

SPECIAL REPORT

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Acute infections of the urinary tract are relatively common in pediatric patients. Experience in the therapy of these infections with the sulfonamides and streptomycin has demonstrated an increasing frequency of failures even though adequate dosages are utilized.[1, 2, 3] Because of the successful results obtained when aureomycin was used in treating this condition,[4] it was decided to utilize chloramphenicol in the treatment of acute urinary infections in childhood.

Chloramphenicol is a crystalline derived from the soil organism, *Streptomyces venezuelæ*, and the drug can be produced synthetically.[5] It has a wide range of activity against both gram-positive and gram-negative organisms.

Pharmacological studies on the excretion of chloramphenicol in human beings have shown that most of an orally administered dose appears in the urine within twenty-four hours; approximately 90 per cent is recovered in the inactive conjugated form.[6]

Hewitt and Williams[7] in a study of thirty-four patients have demonstrated that adequate antibacterial concentrations of chloramphenicol are attained in the urine when therapeutic oral dosages are employed. These same investigators treated twenty-four patients with acute infections of the urinary tract. Three patients failed to show a satisfactory clinical response to chloramphenicol. Garvey, Cline, and Meads[8] utilized chloramphenicol in the treatment of twenty-one patients with pyelitis. All of these patients were adults and only three had acute infections. Thirteen of the twenty-four were classified as therapeutic failures.

* Chloramphenicol ("Chloromycetin") was supplied by Parke-Davis Company, Detroit, Michigan.

† From the Research Foundation of The Children's Hospital of the District of Columbia.

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MATERIALS AND METHODS

At the Children's Hospital during the past year, nine children with acute urinary tract infections caused by a specific organism have been treated with chloramphenicol. There were eight females and one male. The ages of these patients ranged from four months to seven years (Table I). All of

TABLE I

Summary of patients treated with chloramphenicol

PATIENT	AGE	SEX	PATHOGENIC ORGANISM	SENSITIVITY MCGM/CC.	CHLORAMPHENICOL				RESULTS
					mgm/kgm/dose	mgm/kgm/24 hrs.	Total dose	Total days	
	yrs.						*Gms.*		
M. Mc.	4	F.	*Serratia marcescens*	Less than 20	14.0	83.3	12.0	8.0	Urine sterile in 8 days; Recurrence in 2 wks.
L. B.	2	F.	*Escherichia coli*	2 to 5	47.6 23.8	286.0 143.0	25.5	2.7 11.6	Urine sterile in 4 days; *Pseudomonas aeruginosa* cultured from urine in 2 wks.*
P. R.	4†	F.	*Aerobacter aerogenes*	2 to 5	22.7	136.4	4.5	6.0	Urine sterile in 4 days.
N. N.	2½	M.	*Escherichia coli*	5	10.0	80.0	9.5	9.5	Urine sterile in 8 days; *Pseudomonas aeruginosa* cultured from urine in 2 wks.
C. B.	2	F.	*Escherichia coli*	2 to 5	12.5	75.0	7.8	10.0	Urine sterile in 8 days.
L. B.	7	F.	*Escherichia coli*	5 to 10	13.2	79.2	10.8	7.0	Urine sterile in 4 days.
J. S.	6½	F.	*Escherichia coli*	2 to 5	29.5 14.7	176.4 88.2	10.5	1.0 5.0	Urine sterile in 8 days.
J. B.	3	F.	*Escherichia coli*	2 to 5	23.8	190.4	13.5	7.0	Urine sterile in 4 days.
B. T.	6	F.	*Escherichia coli*	2 to 5	13.2	79.2	11.0	7.3	Urine sterile in 8 days.

* Intravenous pyelogram revealed congenital dilatation of both ureters in this patient.
† Months.

these patients had findings referable to the urinary system. These included general symptoms, e.g., vomiting, anorexia, diarrhea, malaise, drowsiness, and convulsions; and specific symptoms, e.g., fever, enuresis, urinary frequency, dysuria, and costovertebral angle tenderness.

On admission a routine urinalysis and complete blood count were performed in every case. A catheterized urine specimen was cultured for predominant organisms and the sensitivity of these pathogenic micro-organisms to chloramphenicol was determined. The patients were followed with daily urinalyses; repeat culture of a catheterized urine specimen was per-

formed four days after the institution of specific therapy and at suitable intervals thereafter. Intravenous pyelography was performed when indicated.

Chloramphenicol was administered orally in all the patients. For the younger patients it was necessary to empty the contents of the capsule and dispense it in a suitable vehicle, e.g., syrup of cherry or syrup of Santa Yerba. The dosage utilized was quite variable ranging from 10 to 24 milligrams per kilogram every three or four hours with an average of 16.4 milligrams per dose. The daily dose varied from 75 to 190 milligrams per kilogram per 24 hours with an average of 106 milligrams. The total dosage administered ranged from 4.5 to 25.5 grams with an average of 10.7 grams. No nausea, vomiting, or diarrhea was encountered during therapy. The duration of treatment ranged from six to fourteen days, the average being eight days.

RESULTS

At the onset of therapy with chloramphenicol a leukocytosis which ranged from 14,600 to 26,200 per cubic millimeter and a shift to the left in the Shilling index was present in seven of the patients. Routine urinalysis revealed a pyuria in each instance. Culture of catheterized urine specimens showed an abundant growth of organisms in every patient. In seven of the group the pathogen isolated was *Escherichia coli; Aerobacter aerogenes* and *Serratia marcescens* were cultured on one occasion each. In vitro sensitivity studies revealed that *Escherichia coli* and *Acrobacter aerogenes* were highly susceptible to small concentrations of chloramphenicol. In no instance were they resistant to a concentration of more than 10 micrograms of the drug per cubic centimeter. The soil organism, *Serratia marcescens,* was found to be sensitive to less than 20 micrograms per cubic centimeter.

The results obtained from chloramphenicol therapy coincided with the in vitro sensitivity findings. In six of the nine patients an excellent outcome was obtained. In each instance the temperature returned to normal and the symptoms disappeared forty-eight hours after therapy with chloramphenicol was instituted. The pyuria cleared comcomitantly with the abatement of symptoms. The urine culture in these patients became sterile by the fourth day of treatment. These negative findings have persisted for two weeks to one month after discharge from the hospital.

An unfavorable outcome was encountered in three patients. One of these was a four year old white female whose urine culture yielded the rare soil organism, *Serratia marcescens.* Although this organism was susceptible to a concentration of chloramphenicol ordinarily obtained in the urine with therapeutic doses, two cultural relapses were observed within one and three weeks after discontinuation of therapy, in spite of transitory sterilization

of the urinary tract. An intravenous pyelogram in this patient revealed congenital dilatation of both ureters. Pool and Cook[9] have pointed out that the most important single factor in the efficacy of any treatment of urinary tract infections is the presence or absence of complications. Other pathological conditions such as anomalies, tumors, stones, residual urine, or foreign bodies must be cared for before the infection can be permanently eradicated. In the remaining two failures the initial infections with *Escherichia coli* were eradicated and symptoms cleared promptly. However, a highly resistant organism, *Pseudomonas aeruginosa*, which required an in vitro concentration of 50 to 100 micrograms of chloramphenicol per cubic millimeter to inhibit its growth, was subsequently cultured from catherized urine specimens. This organism was present despite the absence of pyuria. A similar finding was reported by Garvey and his co-workers[8] who noted the development of relatively resistant organisms in four of the twenty-four cases of urinary tract infections treated by them with chloramphenicol. The exceptional resistance of *Pseudomonas aeruginosa* to all forms of therapy is well-known[7,8]. As yet there is no safe therapeutic agent which is effective in eradicating this organism when it occurs in the urinary tract.

TOXICITY

The gastro-intestinal symptoms which are encountered occasionally during a course of therapy with aureomycin were not noted with chloramphenicol. Glossitis, cheilosis, and vaginitis have been reported with chloramphenicol[10] but did not occur in this small series. One patient, a two year old colored female who had an initial leukocytosis of 17,100 white blood cells per cubic millimeter, developed a leukopenia of 2,800 white blood cells per cubic millimeter eleven days after the institution of chloramphenicol therapy. The development of a leukopenia during a course of treatment with chloramphenicol has been previously reported by other investigators at this hospital[11]. However, the white cell count returned to normal shortly after discontinuation of therapy.

CASE REPORT

The following brief protocol serves to illustrate the course of events in one of the patients in whom a favorable response to therapy resulted.

J. S., a six and one-half year old white female, was admitted to the hospital on August 21, 1949 with a two day history of fever, abdominal pain, and vomiting. On admission the temperature was 104.8°F. Tenderness in the left costo-vertebral angle was the only positive physical finding.

The white blood count was 26,200 per cubic millimeter with 90 per cent neutrophiles and a shift to the left in the Shilling index. Routine urinalysis revealed the urinary sediment to be packed with clumps of white blood cells. Culture of a catheterized urine specimen resulted in a profuse growth of *Escherichia coli* which was sensitive to 2 to 5 micrograms of chloramphenicol per cubic centimeter.

Two days after admission, therapy with chloramphenicol was instituted. The dosage utilized was 500 milligrams orally every four hours for six doses, then 250 milligrams every four hours for the next thirty doses. Diet and fluids were permitted as tolerated.

Forty-eight hours after specific therapy was started the temperature returned to normal, all symptoms had disappeared, and pyuria was no longer demonstrable. Urinary sterilization was attained on the fourth day of therapy.

Two months after discharge from the hospital the patient was still symptom-free and a routine urinalysis was normal.

SUMMARY

Nine children with urinary tract infections (seven of which were due to *Escherichia coli*, one to *Aerobacter aerogenes*, and one to *Serratia marcescens*) were treated with chloramphenicol. The dosage ranged from 75 to 90 milligrams per kilogram per twenty-four hours given at three to four hour intervals. Disappearance of symptoms and pyuria was noted in all nine patients. Two patients on subsequent urine cultures were noted to have developed a relatively resistant strain of *Pseudomonas aeruginosa*. One patient with congenital hydro-ureters relasped following discontinuation of chloramphenicol.

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THE PRESENT STATUS OF PERTUSSIS IMMUNIZATION

Progress Report

William A. Howard, M. D.

From its earliest beginnings, pertussis immunization has had the doubtful honor of being the least effective of the routine immunizing antigens used, and being most likely to cause unpleasant side effects. This was especially true of the original vaccine, a saline suspension of killed bacteria. Modification of the antigen by precipitation with alum, and by combining it with other immunizing agents has materially increased its effectiveness, and tended to decrease the unpleasant side reactions, but in spite of these measures whooping cough prophylaxis remains something of an uncertainty.

Until relatively recently, pertussis vaccine was always given at six months of age or later, either singly or in combination with diphtheria toxiod, or diphtheria and tetanus toxoids. This situation resulted primarily from the generally accepted dictum that the infant under the age of six months has a definitely lessened ability to develop immunity in response to the stimulus of injection of vaccine or toxoid, and that he has a certain amount of immunity to disease as a result of the presence of antibodies passively transferred from the maternal circulation, in the presence of which active immunity response is depressed. The validity of this second point is open to some question since more and more women are reaching the child-bearing age minus protective antibodies to many of the diseases of childhood. In addition there is increasing evidence that even though the immunity mechanism is not fully matured, the injection of a suitable antigen in sufficient quantity does call out an immunity response which may offer a valuable degree of clinical protection.

Current statistics indicate that whooping cough mortality has become primarily a problem of the first year of life. The pertussis death rate in infants under one year of age, although steadily declining in actual numbers, has increased in proportion because of the more rapid decline of the pertussis death rate in older age groups. This can only mean that the younger the child the more vulnerable he is to pertussis, and by the same token, the more unlikely it will be that he has received prophylactic immunization. As a result of these facts it has become necessary to consider just how early we can give pertussis vaccine with safety and success to protect those in whom the danger is greatest.

Numerous studies have been conducted recently to determine the effectiveness of pertussis vaccine at different age levels. Laboratory evidence of successful immunization has been based primarily on the agglutination

response and on the pertussis agglutinogen skin test. Although there is no evidence tht the agglutination reaction plays any part in the immunity mechanism, or that the reaction occurs at all in vivo, agglutination titers of 1:320 or higher definitely appear to be associated with clinical immunity. There also appears to be close correlation between the aggluntination reaction and the aggluntinogen skin test, so much so that the latter may now be used as confirmatory evidence of immunity.

Experimental evidence indicates that three doses of alum precipitated or aluminium hydroxide adsorbed pertussis vaccine when administered at monthly intervals beginning as early as the first week of life, will produce agglutinin responses in more than sixty per cent of the infants treated. However, titers of 1:320, supposedly consonant with clinical immunity, are present in only 30–35 per cent. When the injections are begun at age three months, up to sixty per cent of those treated will develop so-called protective titers. Administration of the vaccine at six months of age or later shows only moderate increases in the percentages giving protective agglutination levels.

It is obvious that even though the immunization procedure is not 100 per cent effective at the earlier ages, there is every reason to expect that some benefit will accrue with immunization of those infants more likely to be exposed to infection. This protection is more than evident in studies so far reported.

The dosage required to produce adequate immunity depends upon the type of material used. In the old saline suspension, at least 100 billion organisms, given in three injections, was required for maximum immunity response. With the use of the newer preparations, as few as 40 billion organisms have produced satisfactory results. There appears to be a direct correlation between the size of the dose, the protective response, and the number of unsatisfactory reactions which occur. One must always compare the toxicity resulting from higher doses with the failures which result from a lower total of bacteria injected. If pertussis vaccine is to be given at any time during the first six months of life, the optimum dose appears to be between 40 and 60 billion cells, given either as the alum precipitated or aluminium hydroxide adsorbed preparations.

Reactions to pertussis vaccine have consisted primarily of local swelling, redness and induration, and fever of varying severity and duration. Normally, these side effects are easily controlled, and constitute no contraindication to the administration of the vaccine. Convulsions and other encephalitic manifestations have occurred often enough and have been sufficiently severe to be considered a problem in the administration of the vaccine. There is definite agreement that active pertussis prophylaxis in any form should not be administered to any child with a history of convul-

sions, and should not be given during the time the child has active infection of any type. In doubtful cases it is appropriate to reduce the dosage and increase the number of injections until the effects of the vaccine can be ascertained.

It is difficult to establish the optimum time for the administration of pertussis vaccine, as evidenced by the almost complete lack of agreement on this point among workers in the field who attempt to outline programs for routine immunization. Whether initial immunizations are attempted at one week, six weeks or later, depends not so much on the effectiveness of the vaccine as on the development of an immunization schedule designed to fit the particular infant or his particular needs. In a more or less sheltered home environment, and in a community where the administration of pertussis vaccine is more or less routine, the physician may safely wait until three to six months of age before beginning prophylaxis. Where high rates of incidence prevail, where probable exposure can be anticipated, or where socio-economic and environmental factors are such as to foster the spread of communicable disease, earlier immunization would appear to be desirable.

PRIMARY ENCEPHALITIS OF UNDETERMINED VIRUS ETIOLOGY

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W. A. N. 50–4622

W. A. N., a ten year old colored male, was admitted to Children's Hospital on August 22, 1949 with the chief complaint of a generalized convulsive seizure which had lasted for two and one-half hours.

The history revealed that the patient had sustained a head injury two months prior to this hospitalization. Except for a mild headache following this traumatic incident, no other abnormalities ensued. He was apparently well until one week before admission to the hospital at which time the child received another head injury. There was no unconsciousness; however, within a few hours headache, dimness of vision, and paresthesia of the right hand became manifest. Dysarthria and thickening of speech was noted at that time. In a short period of time following the administration of two and one-half grains of acetylsalicylic acid all of these symptoms disappeared. The day before admission, the patient complained of a severe, persistent, generalized headache. The following day there was a sudden onset of a generalized convulsive seizure which lasted for two and one-half hours. He was hospitalized following this incident.

The patient was the product of an uncomplicated pregnancy and a normal, spontaneous delivery. The birth weight was nine pounds seven ounces. There had been no neonatal difficulties. He had had uncomplicated measles, mumps, and chickenpox early in childhood. The usual prophylactic immunization procedures had been adequately carried out in infancy. The feeding history was adequate and development had progressed in a normal pattern. Questioning failed to elicit a history of any previous mental abnormalities or neurological disorders in the patient. The possibility of recent ingestion of any noxious agent or exposure to disease were denied.

The family history failed to reveal tuberculosis, venereal disease, diabetes, cancer, or central nervous system diseases.

The admission physical examination revealed a well developed and nourished colored male who was comatose and responded only to deep proprioceptive stimuli. The temperature was 98°F., the pulse rate 62 per minute, and the respiratory rate 15 per minute. The blood pressure was 110 systolic and 80 diastolic. No nuchal rigidity or back stiffness were present. A horizontal nystagmus with the rapid component to the left was noted. There was no abnormality of the corneal reflex. The pupils reacted to light and the consensual reflex was normal bilaterally. Fundoscopic

examination did not reveal any abnormalities. All of the superficial and deep reflexes were absent. An abnormal Babinski reflex was elicited bilaterally. The remainder of the physical examination yielded no other pertinent data.

The initial hemogram revealed a hemoglobin of 10 grams and 3,900,000 erythrocytes per cubic millimeter. The leukocytes numbered 15,400 per cubic millimeter of which 88 per cent were polymorphonuclears and 12 per cent were lymphocytes. The thrombocytes were normal. Repeated urinalyses were within normal limits. The examination of the spinal fluid obtained from lumbar puncture revealed six leukocytes per cubic millimeter, the protein content was fifteen mgms. per cent and the sugar 45 mgms. per cent. The spinal fluid Wassermann and colloidal gold curve were normal. Serological blood tests for syphilis were negative. A series of intracutaneous tests for tuberculosis failed to produce a positive reaction. Repeated blood cultures did not grow any pathogenic organisms. Roentgenographic studies of the chest and skull were interpreted as normal.

A rapid and complete recovery from the initial post-convulsive stupor was made, however, during the first week of hospitalization there were repeated episodes of grand mal seizures. These were adequately controlled by the parenteral administration of phenobarbital. The course had been afebrile but a remittent type of fever with temperature spikes as high as 104°F. became manifest at this time. Physical examination revealed a pharyngo-tonsillitis, and therapy with 300,000 units of procaine penicillin administered daily via the intramuscular route was instituted. Examination of the spinal fluid seven days after admission revealed a pleocytosis of 102 leukocytes per cubic millimeter of which 81 per cent were lymphocytes and 19 per cent were polymorphonuclears. The sugar content was normal but the protein was elevated to 40 mgms. per cent. The spinal fluid pressure was 110 millimeters of water and the Queckenstedt test was normal bilaterally with a 'snail's pace' rise to 140 millimeters of water and a gradual drop to the initial pressure on release of jugular compression. No organisms were cultured from the spinal fluid. Spinal fluid examination was repeated three days later and revealed essentially no change.

The patient complained of pain in both lower extremities and a severe, persistent, generalized headache which was not relieved by salicylate therapy. Pneumencephalography was performed two weeks after hospitalization. The findings from this examination were normal. Despite anticonvulsant therapy with phenobarbital and dilantin sodium, the convulsive seizures increased in frequency. The febrile course remained unaltered ranging from 102°F. to 103°F. In the third week of illness, the patient lapsed into a continuous comatose state and to all observers his condition appeared to be critical.

The patient remained in this comatose state for the next two month period of hospitalization. He was maintained on daily, vitamin supplemented, gavage feedings (1500 calories daily). During this two month interval, as many as twelve tonic-clonic convulsions occurred each day. Constant athetoid movements of all extremities were exhibited during periods of quiescence. Hypostatic pneumonia and atelectasis of the right upper lobe necessitated the almost constant administration of oxygen. Repeated spinal fluid examinations revealed no abnormalities of the cell count, sugar or protein content, or manometric studies.

Eleven weeks (76 days) after the onset of illness the patient began to take small amounts of food when fed from a spoon. He improved gradually and was finally discharged for convalescent care at home three months after admission to the hospital. Two weeks after discharge, the patient walked for the first time although marked ataxia was present. Complete aphasia was present, but he seemed to comprehend when spoken commands were given. Incontinence of feces and urine was present. One month after discharge from the hospital the ability to speak intelligibly returned; bowel and bladder control were regained. Two weeks later (four and one-half months from the onset of illness) a placement test for school revealed the patient's intelligence quotient to be normal for his age. He has been able to remain with his class despite the fact that he had missed the first semester of school. He is normal in all respects, and a complete neurological examination at this writing is entirely within normal limits.

DISCUSSION

The primary virus encephalitides have been classified by Webster and Leschenko as follows:

1. Rabies
2. Poliomyelitis (polioencephalitis)
3. Saint Louis encephalitis
4. Japanese "B" encephalitis
5. Louping ill
6. Australian "X" disease
7. Equine encephalomyelitis—of which there are two serological types of virus, eastern and western.
8. Lymphocytic choriomeningitis
9. Herpes encephalitis
10. Von Economo encephalitis and European encephalitis.

There is some dispute as to whether the herpes virus is capable of producing encephalitis and the etiologic agent of von Economo encephalitis is unknown, though the evidence points towards a viral etiology.

Muckenfuss has described the epidemic encephalitides in which are in-

cluded von Economo encephalitis, Saint Louis encephalitis, Japanese "B" encephalitis, Equine encephalomyelitis (eastern and western types), Australian "X" disease and another form of epidemic encephalitis, Russian encephalitis, not mentioned by Webster. The last mentioned occurs in the spring and early summer in Russia and Siberia and is caused by a virus immunologically different from the viruses of the Saint Louis and Japanese encephalitides.

This discussion will include mainly those viral encephalitides occurring in epidemic proportions, namely those mentioned by Muckenfuss as epidemic encephalitides. It must be kept in mind, though, that there are other forms of encephalitis; the primary ones mentioned above in Webster's classification and the other forms such as post-infectious encephalitis, post vaccinal encephalitis and post rabic therapy encephalitis which will not be discussed here.

Etiology—The disease described by *von Economo* was the first of the group to be recognized, and has been subjected to the most intensive investigation without success in establishing its etiology.

Saint Louis encephalitis is caused by a virus found in the central nervous system of fatal cases, and capable of causing a fatal infection in mice and a non-fatal infection in macacus rhesus monkeys on intracerebral injection and in mice by intranasal instillation. Histologically, the lesions produced in mice and in monkeys are analagous to those observed in humans; the essential pathologic process is an acute, non-purulent inflammation of the central nervous system characterized by intense vascular congestion with petechial hemorrhages, cellular infiltration of both nervous tissue and meninges with various types of mononuclear cells, and evidence of toxic degeneration in the nerve cells. The virus of Saint Louis encephalitis is neutralized by serum from persons who have recovered from the disease and is immunologically distinct from other viruses.

Japanese "B" encephalitis resembles Saint Louis encephalitis and is caused by a virus infectious for mice and monkeys. The Japanese encephalitis virus is neutralized by convalescent serum and is immunologically different from Saint Louis encephalitis virus and other viruses. However, there is some evidence that the Japanese virus may be somewhat related to the Saint Louis virus. Several Japanese investigators have found that serum of rabbits immunized against the Japanese virus neutralized not only the Japanese virus but also the Saint Louis virus.

Equine encephalitis occurs in two forms, the eastern type occurring east of the Appalachian mountains; and the western type occurring west of this mountain range. The two types are immunologically different. A number of animals and birds are susceptible, and some of these have been found naturally infected. These facts may be of considerable epidemiologic importance.

Australian "X" Disease is a form of encephalitis which has also had its etiology ascribed to a virus. Experimentally, by means of intracerebral inoculation of material from the central nervous system of patients who have died of the disease, successful transmission of the infection to monkeys and sheep was reported by Cleland and Campbell.

Russian encephalitis has been described as being caused by a virus to which mice and monkeys are susceptible. The virus appears to be immunologically related to the virus of Japanese type "B" encephalitis, although, the two are distinguishable by cross neutralization tests.

EPIDEMIOLOGY—*Von Economo* encephalitis—numerous epidemics of von Economo encephalitis have occurred throughout the world from 1920–1926, and since that time the incidence has been gradually diminishing. It is reasonable to consider it endemic rather than epidemic. During the epidemic periods the incidence was highest during the winter months, however, during recent years this tendency to seasonal distribution has been less marked. With knowledge lacking concerning the etiology, there can be little certainty concerning the mode of transmission or factors directly affecting the spread of this disease. It has been assumed, though, that the virus is present in the nasopharyngeal secretions and that it is only in the early and prodromal stages of the disease that it may be transmitted. It has also been assumed that healthy carriers play an important part in disseminating the virus.

No age is exempt and it is apparently more prevalent in large cities rather than rural districts.

Saint Louis encephalitis—the epidemic in Saint Louis in 1933 is not the only one caused by this virus. Other possible epidemics of the Saint Louis form were in Paris and Illinois in 1932; in New York City in 1933; in Kansas City in 1933; and a second outbreak in Saint Louis in 1937.

Epidemics have occurred characteristically in the late summer and early autumn. The fatality rate ranged between 20 to 30 per cent and both the incidence and fatality has been high in the older age group.

The etiological virus has been demonstrated only in the central nervous system of fatal cases. The manner of spread of Saint Louis encephalitis is consistent with that for a disease transmitted by droplet infection and by carriers. That mice can be infected by dropping the virus in the nose supports this possibility. Although the virus has never been recovered from nasal washings, there is indirect evidence that it may be present in this location.

Biting insects have been suspected as possible vectors, although the failure to demonstrate the virus in the blood stream makes it difficult to see how they could become infected.

It appears likely that human contact, chiefly through unrecognized carriers, is the method of infection here, but that susceptibility, in which age

is an important factor, determines who will contract the disease in an infected community.

Japanese type "B" encephalitis—epidemologically, Japanese type "B" encephalitis is similiar to Saint Louis encephalitis except that the fatality is higher, over fifty per cent. The virus causes a more severe infection which is fatal in monkeys, and it is also capable of infecting young sheep. It is uniformly present in the blood stream of mice in the early stages of infection. Furthermore, intraperitoneal or subcutaneous injection of the virus more frequently leads to infection in mice than does inoculation of mice with Saint Louis encephalitis virus. There are several reports of isolation of the virus from the spinal fluid of patients; this had not been reported in Saint Louis encephalitis.

Mitamura and his co-workers have shown that mosquitoes may be true resevoirs of the virus and that they are able to transmit the disease to laboratory animals by biting. However, the objection is raised that the number of cases in the towns affected is not in proportion to the distribution of the mosquitoes.

Equine encephalomyelitis—there are at least five immunologically different forms of encephalomyelitis affecting horses. Only the two forms occurring in the United States, the eastern and western types, however, have been proved to infect man, and this discussion is accordingly limited to these two. Although there are differences, the similarities from an epidemiological standpoint are so great that both may be considered jointly.

Both the equine and human cases occur chiefly in the summer months and the human cases usually appear within a district in which the equine disease is prevalent. There is reason to believe that several varieties of mosquitoes act as vectors and that a reservoir of the infection is to be found in birds as well as in horses. The disease among horses is known to have appeared from time to time for at least seventy years, but it was only in 1938 that it was established that man was susceptible. During that year a small number of cases of acute encephalitis in Massachusetts and Rhode Island were shown to be due to infection with the eastern virus. In some seventy per cent of all cases the victim was under ten years of age. During the same year several small epidemics appeared in the middle west which were traced to the western virus. In the west adults were predominantly affected. In 1941 a large epidemic of nearly 3,000 cases developed in North Dakota, Minnesota, South Dakota, Montana, Nebraska, and Manitoba. It is also claimed that the disease is prevelant in South America and Russia.

Australian "X" Disease—during the period of January to April (the warm season in Australia) in two successive years, 1917 and 1918, there appeared in Australia (New South Wales and parts of Queensland and Victoria) a disease with such puzzling features that it was called the "mysterious disease" or "X disease". Cases occurred in isolated country districts

widely removed from each other, with no apparent means of contact between the victims. Nearly fifty per cent of the patients were children under five years of age, males being more often affected than females, and the general mortality was seventy per cent. After further study it became evident that the disease was an acute form of encephalomyelitis, similiar in many respects to the Japanese "B" encephalitis.

Russian encephalitis—this form of encephalitis occurring in the spring and summer in Russia and reported from the laboratories of Smorodintseff by a group of collaborators seems to have the following characteristics:

1. It is endemic in the forest regions and is limited to people working in the forests.
2. It seems to remain in the endemic areas without spreading from them.
3. It does not show the higher mortality in older age groups characteristic of Saint Louis and Japanese encephalitides.
4. Rodents in endemic areas are infected. Some of them show no apparent illness, and the virus appears in the blood stream.
5. Ticks in endemic areas are infected and are capable of transmitting the disease.
6. The virus is serologically related to, but distinguishable from, the virus of Japanese encephalitis.

The Russian observers believe that the disease is one of rodents and that man is only incidentally infected.

Symptomatology and Diagnosis—The symptoms and diagnosis of encephalitis are considered at this point rather than earlier, because epidemological considerations must enter into differential diagnosis.

Von Economo's disease has an acute stage lasting a few days characterized by low fever, dizziness, diplopia, ocular paralyses, and sometimes headache, some stiffness of the neck, and a mild pleocytosis in the spinal fluid usually about fifty cells. The symptoms are variable and in about one half of the cases are so mild as to pass unnoticed or not to suggest encephalitis. It may be months or even years later that the sequelae (or more correctly the chronic stage) make the diagnosis evident.

The course of the disease, although variable in the extreme, classes patients logically into the following groups, according to Josephine Neal:

1. Those that make a complete recovery;
2. Those in whom the disease is progressive;
3. Those in whom there is progression of the disease after some delay; and
4. Those in whom the disease progressed with remissions.

In the chronic stage, contractions, spasticity, mental deterioration, and Parkinson's syndrome are particularly characteristic.

The other types of encephalitis discussed are so similar in their clinical

manifestations in the acute stage that they may be considered together. Although there may be short periods of invasion, the onset is usually sudden, with fever, headache, occasionally vomiting, stiff neck, and pleocytosis in the spinal fluid, usually in the neighborhood of 200 to 300 cells. Mononuclear cells predominate, except apparently in equine encephalitis where neutrophiles seem to predominate.

Differentiation may be made on the following points:

1. Only Saint Louis encephalitis and equine encephalomyelitis have been recognized in the United States.
2. The highest incidence of these diseases is in the late summer and fall.
3. Specific neutralizing antibodies may be demonstrated after recovery.
4. The virus may be isolated from central nervous system in fatal cases and may be identified.
5. Serious sequelae are rather rare after Saint Louis encephalitis, but common after equine encephalomyelitis.
6. Older people are particularly susceptible to Saint Louis encephalitis; this is not true of equine encephalomyelitis.

It should be emphasized that on clinical grounds alone a positive differentiation of the different forms of epidemic encephalitis is not possible. It is only with the aid of the laboratory that this may be accomplished.

There are other forms of encephalitis, for example, postinfectious encephalitis, and other infections of the central nervous system, which may confuse the diagnosis. These must be differentiated in making the diagnosis but are not considered in this paper.

Prognosis—Howe studied sixty-six patients with epidemic encephalitis and found an immediate mortality of eleven per cent. This immediate mortality was highest in the group of children in which the encephalitis was characterized by paralysis or excitation of the somatic or cranial nerves. Recovery was almost invariably encountered when the encephalitis was predominated by signs of meningeal irritation and a relatively high cell count in the spinal fluid. The most dreaded sequel, parkinsonism, ensued most frequently in those cases where the onset of illness was characterized by excitement, bizarre activity, and sleeplessness.

In the cases reported complete incapacity was found in nineteen per cent, partial incapacity in twenty-two per cent, and complete recovery in forty-six per cent. Parkinsonism ensued only after a characteristic type of progressive sequelae, i.e., hyperactivity (usually of a bizarre type), sleep inversion, personality changes, hyperpnea, tics, etc. Non-progressive sequelae, e.g., paralyses, choreiform movements, emotional instability, and mental retardation most frequently followed the type of encephalitis in which the immediate mortality rate was highest. With the exception of mental retardation, this group offered a good prognosis.

TREATMENT—Treatment of all the infections included under the generalization "epidemic encephalitis" is symptomatic and supportive. Lumbar puncture frequently relieves headache, and sedation may be necessary. Relief of the distressing manifestation of the chronic stage of von Economo's disease has been most successful following administration of belladonna derivatives. Many other therapeutic measures have been tried with varying opinions concerning their value.

PROPHYLAXIS—Prophylaxis, in the absence of specific immunizing agents, must depend on general measures. It seems reasonable to isolate patients in the acute stages, to restrict visiting, to have attendants wear masks, to disinfect bedding, discharges, and dishes, and to screen rooms. Screening seems particularly justifiable in areas where equine encephalitis is present in animals. Vaccination of horses against equine encephalomyelitis with formalinized chick embryo vaccine appears to be of value. In man this vaccine has been used with apparent success in laboratory workers intimately exposed to the virus. It is too early to state whether the use of the vaccine under field conditions is advisable.

SUMMARY

1. A probable case of primary encephalitis of virus etiology occurring in a ten year old colored male has been presented.

2. Epidemic encephalitis must now be considered a general term embracing a number of etiologically distinct infections of the central nervous system, which must be identified individually for diagnosis. Since all are so similar epidemiologically, clinically, and pathologically; differentiation is possible only with the aid of the laboratory, where etiologic studies of neutralization tests can be carried out to establish the diagnosis. The manner of spread of these diseases is, for the most part, unknown, but some appear to have a reservoir in lower animals and to attack man through the bite of insects.

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CYANOSIS IN AN INFANT WITH DEXTROCARDIA, SITUS INVERSUS, AND TRICUSPID ATRESIA

Case Report No. 184

Charles L. Waite, M. D. G. L. 50-2209

A case of this type, though rare in occurrence, is presented because it incorporates two more common forms of congenital heart disease and therefore offers an opportunity to discuss them both as they occur singly and concomitantly. It is of further interest because both anomalies may be diagnosed ante-mortem and without the aid of angiocardiograms or other special studies which are at times impracticable in a young infant.

This three month old white male was admitted to this hospital on February 19 with the chief complaint of being "blue." He had been cyanotic since the second day of his life. Initially there had been only circumoral pallor and blueness of the face. Later the condition became generalized and unremitting. Despite the cyanosis the child did fairly well at home, having only an occasional attack of dyspnea. For this reason a cylinder of oxygen was kept in the house to be used during these episodes. On the day of admission the infant suddenly became more cyanotic and developed severe dyspnea which was unrelieved by the administration of oxygen.

Congenital heart disease had been suspected previously, but no attempt was made to ascertain the type of anomaly that existed. No murmur had been heard and a previous x-ray of the chest had been reported as normal. There was no history of convulsions.

The patient was the product of an eight month gestation period which was terminated by a long and difficult labor. The birth weight was 5 pounds, 12 ounces and the weight on admission was 9 pounds, 1 ounce. The maximum weight was 9 pounds, 7½ ounces, one week prior to admission. There was no history elicited of maternal rubella occurring during this patient's gestation. The patient has a sister, two years of age, who is living and well.

Examination on admission revealed an extremely cyanotic white male infant in acute respiratory distress. The temperature was 101.0 F. rectally. There was flaring of the alae nasi, dull injected tympanic membranes, edematous tonsils, and a dusky blue pharynx and oral mucosa. Intercostal retractions were noted, but the lung fields were clear. The point of maximum impulse of the heart was in the fifth right interspace, 5½ centimeters to the *right* of the midsternal line. The heart sounds were best heard in the right chest being almost absent in the left chest. The rhythm was regular and no murmurs were heard. A pulsating mass interpreted as liver was

palpated in the left upper quadrant of the abdomen. The mass had a clearly defined edge which extended 3 centimeters below the left costal margin. Palpation of this mass was very similar to palpation of the radial pulse in the wrist. The heart rate was too rapid to fix the abdominal pulsation as presystolic in time. The remainder of the physical was negative. A tentative diagnosis of dextrocardia, situs inversus, and tricuspid atresia complicated by otitis media and pharyngitis was made.

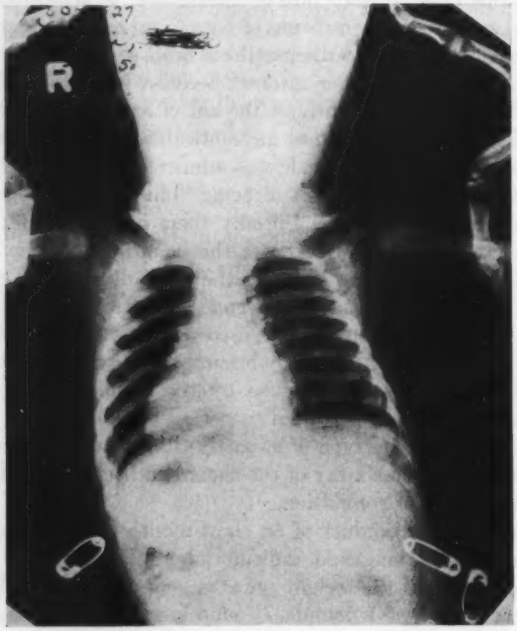

FIGURE 1. G. L. AP view of chest showing dextrocardia, gas bubble in stomach on right, and liver margin on left.

The blood count showed 15 grams of hemoglobin and a normal white cell count. The urinalysis was normal. An x-ray taken on the sixth hospital day confirmed the diagnosis of dextrocardia and situs inversus. Fluoroscopy and barium swallows were also performed. An electrocardiogram on the seventh hospital day was read as dextrocardia with a superimposed left axis deviation.

The otitis media and upper respiratory infection responded promptly to penicillin therapy. The patient was kept in an oxygen tent for one week and at the present time can spend long periods outside his tent. No corrective cardiac surgery is planned in the immediate future.

DISCUSSION

Simple uncomplicated dextrocardia and situs inversus is little more than a medical curiosity. There is no cyanosis, thrill, or heart murmur to make the patient or the physician think anything is awry. Most cases are discovered by mass x-ray surveys, armed forces examinations, and exploratory laparotomy. There are no abnormal shunts of blood from left to right and therefore no cause for cyanosis. For this same reason there is no murmur or thrill.

In 1915, Moffett[1] reviewed the reported cases of dextrocardia and situs inversus and found the first reported case to be in 1649. A total of 115 cases were reported in the literature between 1649 and 1915. Manchester and White[2] in 1938 reviewed the history of reported cases of dextrocardia since the time of Aristotle[3] who first noted complete situs inversus in animals. Contrary to Moffett's date, Fabricium, 1606 and Severinus[4], are given credit for recording the first cases noted in humans. Two cases were reported by Riolanus[5] in the seventeenth century, one of them being Marie de Medici. Senac[6] in 1749 was the first to differentiate between congenital and acquired dextrocardia. Jaccard[7] in 1920 found 61 reported cases proven by autopsy between the years 1887 and 1920. He also made the observation that pulmonary stenosis and interventricular septal defect was not uncommonly associated with complete heterotaxia.

It has been often stated that the incidence of dextrocardia and situs inversus is higher than is commonly suspected. Lewald[8] in 1925 reported that certain groups screening men for duty during World War I had noted an incidence as high as one in three thousand. His own personal observations were recorded as follows:

Dextrocardia and Situs Inversus	*Incidence*
Diagnosed by x-ray	1 in 1,400
Post-Mortem examination	1 in 5,000
At the dissecting table	1 in 10,000
Diagnosed by routine physical	1 in 35,000

Parsons[9] in 1945 reported two cases in 15,000 private patients examined by x-ray. Caplan[10] of the United States Public Health Service, using the 35 millimeter film photofluorographic screening technique, reported 12 cases in the first 100,000 personnel x-rayed. Eight of these were confirmed by further examination and electrocardiographic studies. None of these patients had any symptoms or signs. His confirmed incidence for the series was 0.008 per thousand. Richman[11], examining army personnel during World War II, reported an incidence of 3 cases in 15,000. In Abbott's one thousand cases of congenital heart disease proven by autopsy, 29 were isolated dextrocardia, i.e., without any abnormal arteriovenous shunts

DIAGNOSIS: The diagnosis may be made by clinical, roentgenographic, and electrocardiographic findings.

1. *Clinical:* Palpation and auscultation are the most important features in the clinical diagnosis. Percussion of the cardiac silhouette, especially in a small infant is not too reliable. Palpation of the point of maximal impulse which is found in the midclavicular line of the fourth or fifth *right* interspace may frequently be the first clue and on auscultation the heart sounds will be distant or absent on the left side and startlingly clear on the right. In a young child or infant the ease of palpation of the lower margin of the liver under the *left* costal margin should make the examiner aware of a possible situs inversus. If there happens to be an associated enlargement of the liver or spleen then the diagnosis is facilitated. Jaccard[7] stated that in males with situs inversus the right testicle was descended more than the left, and that people with situs inversus were more often left-handed. This has not been substantiated in other more recent series.

2. *Roentgenographic:* Fluoroscopy should be used in preference to a chest plate in the accurate diagnosis of dextrocardia, because there is no chance of the right and left markings being overlooked and the plate being read as normal. This error has been reported by numerous authors. Once a right-sided heart has been visualized, the roentgenologist has only to lower the viewing screen to ascertain the location of the liver. If the patient is given a swallow of barium, the esophageal curves will help decide to which side the aortic arch curves, and whether or not the stomach is reversed. Permanent pictures should be taken for the proper reading and recording of the cases. Vehsemeyer[12] in 1897, was the first to discover a dextrocardia by the use of x-ray. X-ray is still the primary means of discovering this anomaly.

3. *Electrocardiographic:* The electrocardiogram in dextrocardia is pathognomonic. The first case of dextrocardia diagnosed by this means was reported by Waller[13] in 1889. The typical picture of the findings is as follows:

a. Lead I is the mirror image of a normal tracing with the P, QRS, and T waves inverted, but the sequence remaining the same.
b. Lead II resembles the normal Lead III and Lead III in turn resembles the normal Lead II.

These findings are excellently discussed by Taussig[14] and Shepard and Stewart[15].

The electrocardiogram of the case presented is shown in Figure 2.

Dextrocardia is usually classified as an acyanotic type of congenital heart disease[16]. It may be further classified into two main groups, the mirror and non-mirror, each occurring with the same frequency. In the non-mirror type there has been a complete or partial rotation of the heart without inversion of the chambers. There is frequently some serious congenital anomaly associated with this type[17] and the prognosis depends

on the concomitant anomaly and not the dextrocardia. The mirror type is the mirror image of the normal heart with inversion of the chambers and is almost always associated with situs inversus. A right aortic arch is normal for this type of dextrocardia. A mirror type dextrocardia can occur without situs inversus and when this condition exists there is frequently some serious congenital defect which complicates the picture. A case of this nature was discussed by Dr. Bernice Wedum in an earlier issue of *Clinical Proceedings of the Children's Hospital*[18]. Taussig states that in her experience there has been a relatively high incidence of associated anomalies in dextrocardia associated with complete situs

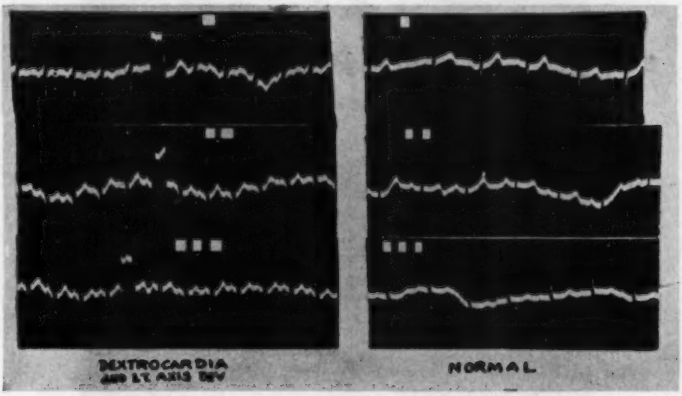

FIGURE 2. G. L. Showing electrocardiogram of patient presented. Normal electrocardiogram on right for comparison.

inversus, and cites several cases. One of these was a transposition of the great vessels and the others were auricular septal defect and re-rotation of the heart back to the left. The case presented falls into this category.

In Maude Abbott's report of 1,000 cases of congenital heart disease proven by autopsy[16] 29 cases of dextrocardia were found. Of these, 11 were associated with situs inversus, 10 without situs inversus but inversion of the chambers, and 8 without either.

Tricuspid atresia is a type of congenital heart disease which produces persistent cyanosis. The right ventricle is usually small, non-functioning, or absent; and the tricuspid valve is atretic or absent. The pulmonary conus is stenosed and non-functioning because of its origin from the right ventricle and therefore, the normal route for the blood to travel to the lungs for oxygenation is lacking.

The blood must travel from the right auricle to the left side of the

heart via a patent foramen ovale or inter-auricular septal defect. It then passes to the left ventricle and out through the aorta passing via the patent ductus arteriosus to the pulmonary arteries. Obviously the patency of the ductus arteriosus is the most important factor necessary for survival. When this closes the patient succumbs. The average duration of life in a patient with this anomaly is from three to four months.[14]

The size of the inter-auricular septal defect determines whether or not

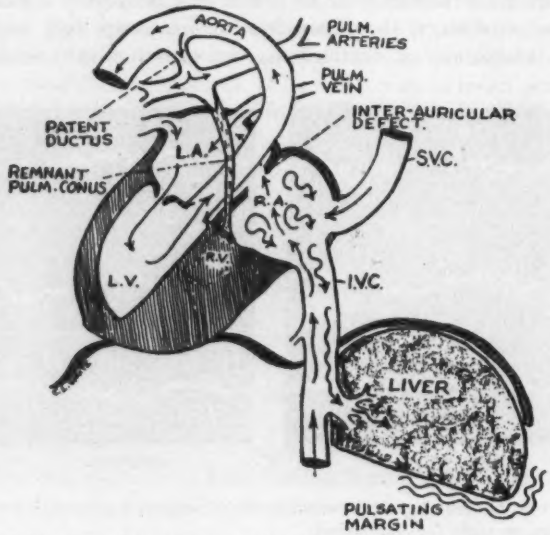

FIGURE 3. G. L. Dextrocardia and tricuspid atresia. Diagram showing the probable course of blood through the heart of the patient presented. An attempt is made to show the mechanism producing a pre-systolic liver pulsation due to a well formed auricular septum and small septal defect.

there is a pulsation transmitted to the liver and also its intensity. If the opening is small, the blood from the venae cavae emptying into the right auricle will be dammed up and the beating heart will relay its pulsation (see Figure 3). The larger the opening the less intense the transmitted pulsation. In cases where there is a complete absence of the septum, there is no pulsation. When a pulsation is present, due to tricuspid atresia, it will be presystolic in time. If the heart rate is too rapid, timing will be impossible and fluoroscopy may prove to be of value.

There may or may not be a heart murmur. If a murmur is heard it is not of diagnostic significance.

Tricuspid atresia is the only type of persistently cyanotic congenital heart disease in which the electrocardiogram shows a left axis deviation.[14, 17, 22]

A review of the literature by Robinson and Howard in 1948[17] showed that there were only 34 cases of tricuspid atresia reported up until 1946. Abbott[16] found 25 cases in her series of 1000 patients.

The diagnosis of the heart lesions in the case presented can be considered now that its two components have been discussed:

1. Dextrocardia with situs inversus has been substantiated clinically, roentgenographically, and by an electrocardiogram.

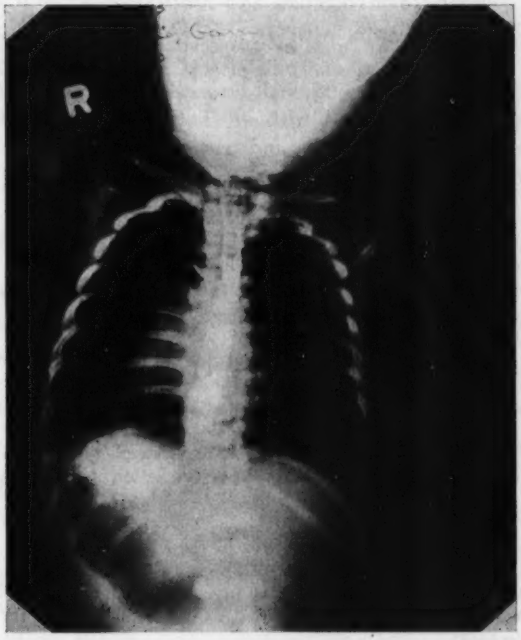

FIGURE 4. G. L. AP view of chest with barium swallow outlining esophagus, showing indentation of right esophageal margin due to a right aortic arch.

2. The patient has the triad of persistent cyanosis, a pulsating liver margin, and a left axis deviation as shown by the electrocardiogram which Nelson[22], Taussig[14] and others state is pathognomonic of tricuspid atresia and a non-functioning right ventricle.

Although a review of the literature revealed no specific cases of this nature, this type of lesion associated with dextrocardia was mentioned by Taussig in 1947[19] in an article dealing with malformations of the heart amenable to the Blalock-Taussig operation.

Cyanosis occurring with dextrocardia is not uncommon. The presence

of a left aortic arch is the most common cause. This is ruled in or out by a barium swallow and a posterior-anterior x-ray view of the chest. A left aortic arch will indent the esophagus on its *left* margin. Such an anomaly was ruled out in this case, a barium swallow showing the esophagus to be indented on its *right* margin (See Figure 4).

There are cases reported of the Tetralogy of Fallot[20] and the complex of Eisenmenger[21] occurring with dextrocardia and causing persistent cyanosis.

CONCLUSIONS AND SUMMARY

1. A case of dextrocardia with situs inversus and tricuspid atresia is presented.

2. It is felt that the diagnosis can be made with reasonable certainty without angiocardiograms and without the patient coming to autopsy.

3. Dextrocardia, situs inversus, and tricuspid atresia are discussed and the literature is reviewed.

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ADDENDUM

Since the writing of this paper the patient expired and the findings at necropsy were briefly as follows:

Dextrocardia with situs inversus
Absence of tricuspid valve
Absence of pulmonary valve
Absence of right ventricle
Patent ductus arteriosus
Patent foramen ovale
Fibrosis of the myocardium
Thrombosis of ductus arteriosus
Thrombosis of left coronary artery
Fibrosis of the spleen
Fatty infiltration of the liver.

The body was that of a well developed, well nourished white male which weighed 3572 grams and measured 44 centimeters in length. There was complete situs inversus of all organs.

The heart measured 6.5 by 6.0 centimeters and the apex extended 4.5 centimeters to the right of the midline and 2.0 centimeters to the left of the midline. The course of the circulation was the same as for for a levo cardium showing the same abnormalities. The venae cavae lay to the left of the midline and the aorta lay to the right of the midline. The venous return entered the right atrium which was dilated and from there passed through a 1.5 centimeter patent foramen ovale. The blood then flowed

through a normal mitral valve which was 7.0 centimeters in circumference and passed into a greatly dilated left ventricle, the wall of which measured 0.4 centimeters in thickness. From there it passed through a normal 4.2 centimeter aortic valve into the ascending aorta which measured 1.3 centimeters in diameter. At the level of the inominate artery on the posterior surface of the aorta, an 0.3 centimeter diameter ductus arteriosus arose which allowed the blood to flow into the 0.6 centimeter left branch of the pulmonary artery and from there into the lungs. The right branch of the pulmonary artery measured 0.4 centimeters in diameter. The pulmonary artery just before its bifurcation measured 0.2 centimeters in diameter and tapered into a fibrous cord which was attached to the base of the heart at the site of its normal origin. The tricuspid and pulmonary valves as well as the right ventricle were entirely absent. Completely occluding the lumen of the ductus arteriosus there was an organizing blood clot. This clot prevented the nonaerated blood from reaching the lungs. Pulmonary venous return and the coronary arteries were normal.

The actual cause of death in this patient was, no doubt, due to the sudden obstruction of the ductus arteriosus. This obstruction closed the principal pathway by which unoxygenated blood reached the lungs, thus abolishing pulmonary circulation.

CLINICO-PATHOLOGICAL CONFERENCE

Directed by: E. Clarence Rice, M.D.
Assisted by: William M. Crowell, M.D.
Francis J. Troendle, M.D.
By Invitation: William F. Burdick, M.D.

William M. Crowell, M.D.

The patient, an eleven month old white male (born January 10), was first admitted on December 15 to investigate the cause of jaundice, weight loss, and weakness, all progressive since August of the same year.

There had been no change in the color of the feces. The urine did not stain the diapers. On physical examination, the skin had poor turgor and a lemon-yellow color; the anterior fontanelle was depressed; the subcutaneous tissue was minimal; the eyes were sunken; slight scleral icterus was present; the pharynx was mildly injected; rales were present in the lungs posteriorly and a mitral systolic murmur was heard. The remainder of the examination was non-contributory. The weight was thirteen pounds, six ounces and the temperature ranged between 99.4°F. and 100°F. Laboratory examinations disclosed: an icterus index of 2 units, the qualitative van den Bergh gave an indirect reaction, the quantitative van den Bergh gave a result too low to read, a corrected sedimentation rate of 36 millimeters per hour, and a normal fragility test. Stools during this admission were yellow. The child was discharged on December 17 without a definitive diagnosis having been made and was scheduled for readmission after a week-end at home.

The past history revealed a normal spontaneous delivery and birth weight of seven pounds. Development was normal until August. Dietary history revealed an adequate intake of protein, fat, carbohydrate, minerals, and vitamins. The parents were of north European stock.

The child was readmitted on December 19 with the physical examination being essentially unchanged except for absence of rales in the lungs, a palpable liver edge one centimeter below the costal margin in the right midclavicular line and hypoactive deep tendon reflexes. Roentgen examination of the skull revealed "a very fine mosaic appearance of the cranium." Long bone examination showed "destructive changes in all bones with some fragmented fractures at the ends of the humeri and femora." The spongiosa was irregularly destroyed, deformed, trabeculated and widened. The corticalis showed thinning. Fluoroscopic and radiographic study of the entire gastro-intestinal tract was normal in all respects.

The chest film disclosed fragmentation of the ends of the clavicles and

scapulae with a widening of the costochondral junction. No cardiac or pulmonary changes were noted.

The following results were reported by the laboratory: Mazzini and Kahn negative for the patient and his parents; a repeat fragility test gave normal results and a stool culture was negative for pathogens. A hemogram after transfusions showed 14.1 grams of hemoglobin, 5.0 million erythrocytes, 11.5 thousand leukocytes, 108 thousand platelets (Rees-Ecker method),

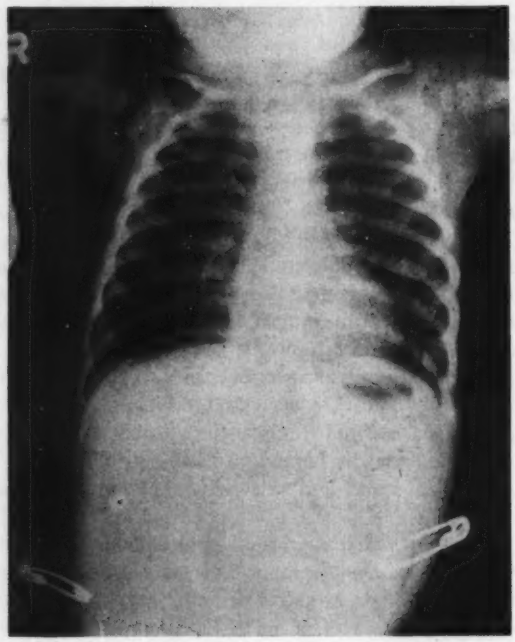

FIGURE 1. S. K. X-ray of the chest showing flaring at the distal end of the ribs

76 per cent granulocytes (68 per cent segmented neutrophiles, 1 per cent eosinophiles), 23 per cent lymphocytes, 1 per cent monocytes, and a rare spherocyte. A bone marrow aspiration showed diminished megakariocytes with normal platelets, and erythroid/leucoid ratio of 1:15 (normal 1:4–1:6), 42 per cent granulocytes of normal distribution, 57 per cent lymphocytes of which 4 per cent were prolymphocytes, 1 per cent monocytes, and a rare spherocyte was present with erythrocytes ranging from normal to microcytes without hypochromia. The interpretation was that of a secondary hypoplasia of the erythroid elements with an increase in

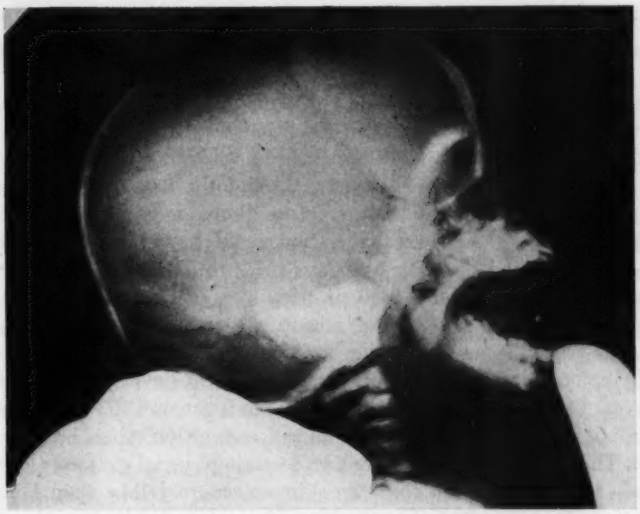

FIGURE 2. S. K. X-ray of the skull showing rarefaction of the bony cranium

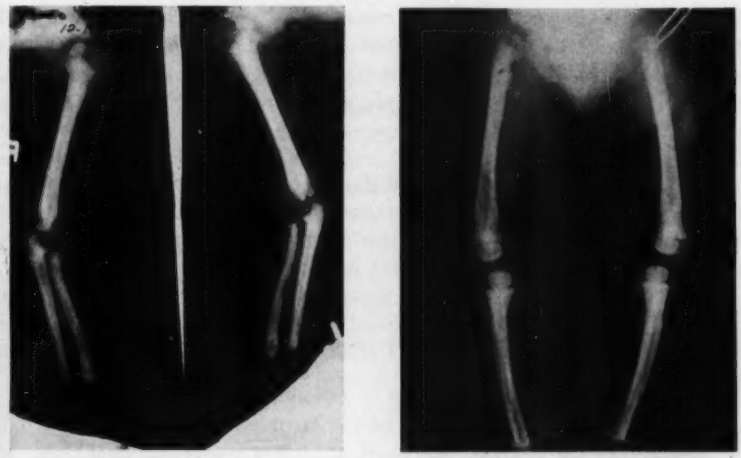

FIGURE 3. S. K. X-ray of the upper and lower extremities showing long bone rarefaction.

the lymphocytic elements and an apparent reduction in the megakariocytes. A hemogram on the day of discharge, December 27, showed 16.5 grams of hemoglobin, 5.0 million erythrocytes, 10.2 thousand leukocytes, 48 per

cent neutrophiles (39 per cent segmenters), and 52 per cent lymphocytes. On the same day a blood calcium was 11.5 milligrams per cent and a blood phosphorous was 17.6 milligrams per cent.

During this second hospital stay (December 19 to December 27), the temperature was irregular with an elevation about every other day from 100.6°F. to 101.4°F. The weight remained at thirteen pounds, eight ounces on two occasions. The appetite was good and the food and liquid intake was normal for this age group. Just before discharge rales appeared in the lungs and the mother reported that he had a cold; however, the temperature was normal and had been for two days prior to discharge. The discharge instructions recommended a high protein, high vitamin intake with liver extract and vitamin B_1 to be administered parenterally, twice weekly. Numerous transfusions were given for the anemia.

At home on the evening of discharge, the patient developed a rhinorrhea and fever. In the morning, December 28, the fever was 103 F. and he was in extremis. He was having a generalized convulsion when he was readmitted. The patient expired before an adequate physical examination could be made but it was noted that the skin was more yellow than before. A urine specimen was collected at the time of death and this showed: appearance—slightly cloudy; reaction—acid; specific gravity—1.005; protein—150 milligrams per cent; sugar, acetone and diacetic acid-absent; 0–2 erythrocytes, 3 leukocytes, 30–40 cell casts, and 8–15 epithelial cells per high power field.

DISCUSSION

William F. Burdick, M.D.

Here we have a case which is difficult to fit into any definite clinical picture due to the paucity of laboratory studies. We must piece together what we have and try to narrow the diagnosis down to one or possibly several conditions which the patient might have had.

The patient obviously had an anemia which was very destructive in character for he had to be transfused many times. Let us consider the diseases which might cause this. I shall group them in three categories and rule out all that I can:

A. Hemolytic Anemias
   1. Erythroblastosis
   2. Sickle cell anemia
   3. Congenital hemolytic icterus
   4. Pernicious anemia
   5. Mediterranean anemia (Cooley's)

B. Malignancy
   1. Leukemia
   2. Neuroblastoma

C. Infections
1. Hereditary syphilis
2. Tuberculosis
3. Malaria
4. Sepsis
5. Liver abscess or chronic hepatitis
6. Chronic kidney infection with renal rickets.

Erythroblastosis is not a likely diagnosis for the child did well until eleven months of age. I have never seen a patient with an anemia due to the Rh factor which was active at the age of this patient. Neither have I seen one without enlarged liver and spleen.

Sickle cell anemia is very destructive and characterized by many hemolytic crises. It has been reported in Greek and Italian children and I believe authenticated. We think of it, however, as being limited to the colored race. The red cells did not show sickling in this case, nor was there a palpable spleen or liver. Even though from northern European stock, he could have had Greek or Italian blood in him.

Congenital hemolytic icterus is another possibility. It is characterized by icterus, palpable spleen and spherocytes in the blood smear. Even though icterus is mentioned in the protocol we must consider the color of the skin and sclerae as due to some other pigment for the icterus index was only two units. We cannot have clinical jaundice without an index of at least fifteen. Here again the normal spleen and liver do not suggest this picture. The fragility test was normal.

Mediterranean anemia is characterized by hemolytic crises and by certain bone changes which could be met in this case. A search through pediatric and x-ray text books for characteristic bone changes in this disease makes me suspicious even though they are not typical. The "hair-on-end" appearance of the skull was not present in this case although the patient might not have lived long enough to develop this picture. The spleen and liver are large in this disease but were normal in this patient. Target cells abound in the blood smears of this disease but there is no mention of them in the protocol.

Leukemia often gives us a picture of bone destruction and osteomyelitis. The bone marrow studies in this case do not fit well into the picture.

Neuroblastoma arises primarily from the adrenal gland, lumbar or retropleural sympathetic tissue. It readily metastisizes to bone. The skin of these patients is pale usually and not icteric. I have not seen the terrific blood destruction in neuroblastoma which was noted in this child. No tumor cells were reported in the bone marrow studies.

This brings us to the infections which destroy blood, cause bone changes, and kill the patient.

Hereditary syphilis can cause a great deal of bone destruction and anemia. This child probably did not have syphilis if the Kahn and Mazzini tests can be relied upon.

Tuberculosis is a low grade, long drawn out infection but I have not seen a case with this much blood destruction. The tuberculin test was negative.

Malaria can be the cause of great blood destruction but I do not know of bone changes occurring. The patient did not have recurring chills and the spleen was not enlarged as it is in malaria with blood destruction.

Sepsis could destroy blood and cause bone changes as well. Some hidden form of infection in the liver or kidneys could cause the lesions in this case.

Liver abscess or chronic hepatitis should be accompanied by an enlarged tender liver with jaundice which this patient did not have.

There are a few clues in this case which point to a kidney as the focus. The patient terminated in convulsions and the urine contained albumin and casts. Uremia could have been present.

I am reminded of a case that I have seen in another hospital with a yellow tinge to the skin. Bone changes similar to these, a high non protein-nitrogen, and chronic kidney disease. He is also dwarfed. The diagnosis of his case is renal rickets.

We know that the genito-urinary tract is subject to anomalies more than any other system. In difficult pediatric cases I have come to think of the urinary tract as causative even though the symptoms are referred elsewhere.

I have in mind a patient I saw at another hospital several years ago. The infant was born prematurely and did well for several weeks then began to run a fever, following which edema was noted. He died in convulsions. The urinalysis prior to death showed albumin and casts. At autopsy there was no functioning kidney tissue left. He died in uremia.

In this case the bone changes and pigmented skin could be explained on the basis of renal rickets. The blood phosphorus is very high and the demineralization of the bones further suggests renal rickets. The low specific gravity of the urine 1.005, 150 milligrams of albumin, and 30 to 50 casts suggest failing kidney function. The convulsive death suggests uremia. A congenital malformation affecting both kidneys, a lesion at the lower end of each ureter such as congenital valves, or a lesion at the bladder outlet could through chronic stasis have been responsible for such a picture.

I believe that I have ruled out everything except a low grade, long standing sepsis and kidney lesions which in turn set up the condition of renal rickets. I favor this diagnosis with a congenital defect in both kidneys or low enough in the urinary tract to involve both kidneys secondarily.

Joseph M. LoPresti, M.D.: I would like to stress how often the urinary

tract is overlooked as a source of pathology in the pediatric age group. I agree with Dr. Burdick that this represents a case of renal rickets. Such a diagnosis adequately explains the entire clinical picture including the increased blood phosphorous and normal blood calcium levels. In the pathogenesis of renal rickets, the basic pathology lies in the urinary tract. This pathology results in chronic renal insufficiency. With renal insufficiency, there is a mild acidosis produced which results in an increased ionization of calcium in the blood stream and therefore, calcium is excreted in the urine in large amounts. Concomitantly with decreased blood calcium, an increased blood phosphorous results. As the blood phosphorous increases, there is an increase in its excretion into the gastro-intestinal tract as inorganic phosphates. Calcium which is ingested in the normal diet combines with these inorganic phosphates in the gastro-intestinal tract to form insoluble calcium phosphate. The patient is thus deprived of his normal exogenous source of calcium, an additional factor in the production of renal rickets. According to some authorities, the increased blood phosphorous in renal rickets acts as a stimulus on the parathyroid glands. The parathyroid glands hypertrophy and as a result of their increased activity produce a mobilization of calcium from the skeletal system into the blood stream. Therefore, insofar as calcium is concerned, there is a balance between the overactivity of the parathyroids on one hand and renal excretion of calcium on the other. This accounts for the normal or near normal blood calcium in renal rickets. Terminally, as renal insufficiency progresses, this balance is disturbed. Large amounts of calcium are excreted in the urine and the patient presents a picture of true hypocalcemic tetany. Whether the terminal convulsion in this patient was due to hypocalcemia or uremia is difficult to say. Most commonly the underlying renal pathology in renal rickets is a congenital anomalous obstruction in the urinary tract ultimately leading to hydronephrosis. Other less common causes are interstitial nephritis, polycystic kidneys, atrophy of the kidneys, or any other condition which produces a longstanding chronic renal insufficiency.

PATHOLOGIC DISCUSSION

E. Clarence Rice, M.D.: The body was that of a poorly nourished white male which measured 67 centimeters and weighed 5.7 kilograms. The circumference of the head was 41 centimeters and the thorax 35 centimeters. The abdomen was markedly distended and had a doughy feel. A number of small petechiae were visible in the suprapubic region. The skin and conjunctivae had a canary color. Marked beading of the costochondral junctions and a Harrison's groove were noted.

The viscera were in normal relationship and no fluid was present in the

pleural or peritoneal cavities. The contents of the thorax presented no unusual abnormality.

The thymus and thyroid gland were normal, however, an enlarged parathyroid gland was found.

The liver and spleen were grossly normal.

The entire gut down to the descending colon was distended with gas. A Meckel's diverticulum was found in the ileum.

After removal of the gastrointestinal tract, there still remained what

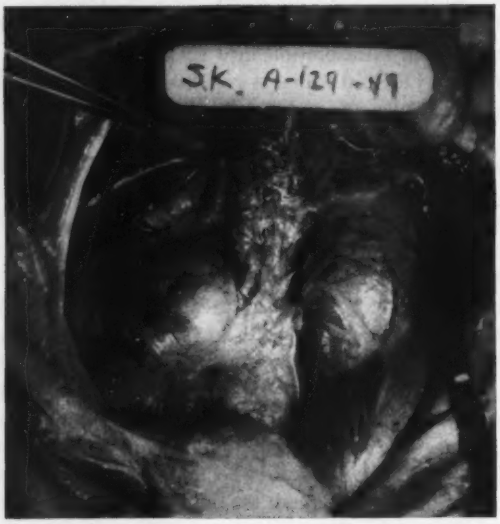

FIGURE 4. S. K. Photograph taken at autopsy after intestines had been removed showing the tortuous, dilated ureters in situ. The tip of the pointer is resting on the small left kidney.

appeared to be several loops of bowel. On further examination these were found to be markedly dilated ureters. The major pathology lay in the genitourinary tract.

The right kidney measured 6.0 x 3.0 x 2.5 centimeters. Numerous cysts varying in size from 1 to 10 millimeters in diameter projected from its surface. The cortex was narrowed; the pelvis, dilated with prominent calyces. Several small cysts were visible in the parenchyma which was of a gray-white color. The right ureter measured 1.0 centimeters in diameter at the uretero-pelvic junction but widened to 3.0 centimeters distal to this point. Ten centimeters from the kidney the diameter of the ureter narrowed to 1.2 centimeters and at this point twisted on itself. At the uretero-vesicle junction the diameter was 0.8 centimeters.

The left kidney was very small, measuring 3.5 x 1.5 x 1.5 centimeters. Section revealed marked cortical narrowing, the major portion of the organ consisting of pelvis and calyces. The left ureter was markedly dilated and at the uretero-pelvic junction its diameter was 1.5 centimeters. It widened to 4.0 centimeters just distal to this point, then narrowed to 0.9 centimeters in diameter. Beyond this point it widened again, twisted upon itself and then narrowed to a diameter of 0.8 centimeters at the uretero-vesicle junction.

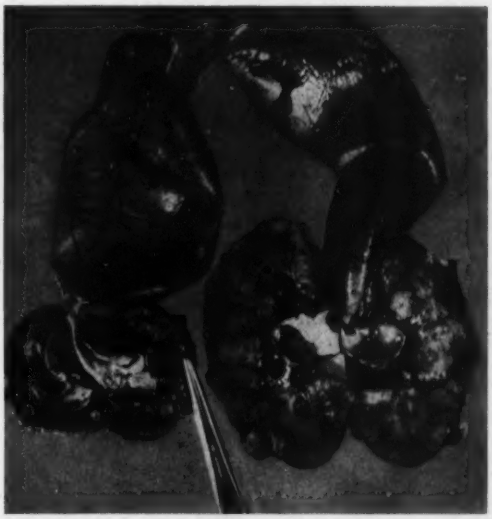

FIGURE 5. S. K. The photograph of the sectioned kidneys with attached ureters showing hypoplasia of the left kidney and numerous cysts throughout both kidneys.

The bladder was large and thick-walled. It measured 5.5 centimeters in diameter and the wall was 0.4 centimeters in thickness. Urine coud be expressed into the bladder from the ureters by compressing the latter.

The prostatic urethra was greatly narrowed so that a probe could not be passed from the bladder through the urethra, although water could be injected from the urethral meatus into the bladder. The remainder of the urinary tract appeared to be normal.

The valve-like structure acted at the prostatic portion of the urethra to cause some obstruction to the passage of urine. The narrowing at the midportions of the ureters and at the uretero-vesicle junctions may have also contributed to the obstruction of the passage of urine.

The adrenals were of normal size but were brighter yellow in color than normal.

The brain was cyanotic in appearance, the superficial blood vessels being engorged. Multiple petechiae were present over the entire surface and free blood was present in the dependent cistern. Coronal sections revealed a partially collapsed ventricular system and both the gray and white matter were congested and cyanotic.

Microscopic examination disclosed deposition of calcium in the thymus, heart muscle, adrenals, and kidneys.

The thyroid gland was normal but the parathyroid gland was hyper-

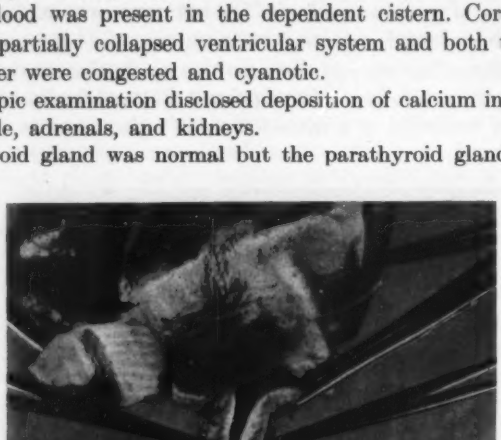

FIGURE 6. S. K. Photograph of the open bladder and ureters showing the valve-like structure in the posterior urethra (see arrow).

plastic. The thymus showed calcification of Hassall's corpuscles and an area of calcification involving the parenchyma.

The lungs were normal.

The heart muscle was normal in some portions, others were the sites of calcium deposition with evidence of necrosis in the adjacent tissue. Several small blood vessels had undergone sufficient calcification of their walls as to have caused obliteration of their lumina. Polymorphonuclear leukocytes have infiltrated some areas and an increase in connective tissue between some of the muscle bundles was observed.

The polygonal cells of the liver were swollen causing sinusoidal compression, and slight calcification of the walls of a few capillaries was noted.

The spleen showed an increase in the supporting connective tissue.

The pancreas and gastro-intestinal tract were normal except for the presence of a Meckel's diverticulum.

A number of areas of calcium deposits were found in the cortex and medulla of the adrenals. Some slight scarring of the fasicular zone with variation of the cell nuclei and cytoplasmic changes in the glomerulosa were present. Medullary congestion with possible slight hemorrhage in one area was seen.

In the right kidney the glomeruli were markedly distended, some being small due to compression from the adjacent fibrous tissue, others were large. A few exhibited early degeneration and partial hyalinization. The tubules varied in size, some having formed large cysts, some were compressed, others tortuous. Hyaline material was present in many of their lumena. Focal accumulation of round cells was present in some portions of the cortex. The walls of the small blood vessels were markedly thickened and their caliber reduced. The capillaries and veins were engorged with blood. Accumulation of calcium was found in the glomeruli and tubules.

The glomeruli and tubules of the left kidney were markedly compressed and distorted due to the excess of connective tissue throughout. But few glomeruli were recognizable and these showed increased fibrosis or complete hyalinization. Many of the changes noted in the right kidney were present in the left.

The brain was congested and the meningeal vessels dilated; some extravasation of blood into the subarachnoid space was observed.

Bacteriological examinations showed that culture of the cisternal fluid and bladder urine revealed no growth.

Post-mortem blood chemistry showed: non-protein nitrogen, 243 milligrams per cent; inorganic phosphorus, 17.6 milligrams per cent; and alkaline phosphatase, 6.2 Bodansky units.

Pathological diagnoses:

1. Atrophy of the left kidney and cystic degeneration of right kidney with bilateral hydro-ureteronephrosis due to obstruction by a congenital valve in the prostatic urethra
2. Calcinosis of thymus, heart muscle, adrenals, and kidneys
3. Renal osteodystrophy
4. Parathyroid hypertrophy
5. Degeneration of adrenals due to 2
6. Meningeal hemorrhage
7. Meckel's diverticulum.

It has been our experience that marked urinary tract pathology in young children may go unrecognized by parents and physicians, and may only be discovered terminally or at necropsy. The importance of a urinalysis is certainly brought out in this case. We are all aware of the difficulties of obtaining a specimen for examination as it was in this patient.

The prolonged urethral obstruction caused hydronephrosis and renal damage of such degree as to cause kidney insufficiency, phosphorus retention, disturbance in available serum calcium, acidosis, and secondary hyperplasia of the parathyroid glands. Bone changes which roentgenologically are indistinguishable from rickets but microscopically are identical with osteitis fibrosa generalista are seen in patients who have had prolonged renal damage with phosphate retention. The parathyroid hypertrophy and hyperplasia represents an effort on the part of the body to compensate for the deranged calcium-phosphorus equilibrium. The calcification noted in this patient is more likely to be seen in primary hyperparathyroidism than in the secondary type. The anemia which was first observed could be attributed to the marked renal impairment and uremia and their effect on the bone marrow.

Mitchell-Nelson's Pediatrics—Edited by Waldo E. Nelson, M. D., Professor of Pediatrics, Temple University School of Medicine, Philadelphia, with the collaboration of 63 contributors, 1658 pages, 7″ x 10″ with 426 illustrations 19 in color. $12.50. New 5th Edition, published February 1950.

The Mitchell-Nelson Textbook of Pediatrics is, without question, the outstanding book in its field. The popularity with which the 1949 edition was greeted will be furthered with the latest edition because of the rapidly changing aspects of periatric therapeutics. An indication of the esteem in which this book is held was attained last year when the senior clerks of Georgetown and George Washington Medical Schools voted this book to be the most popular textbook they had studied in their four years of medical school.

In that connection, Bill Nelson was voted the individual who had done more to solidify and further pediatric education than any other figure. These compliments are quite well deserved and the 1950 edition of this well written book represents the best in textbook writing, being authoratative in its descriptions and therapy with deletion of much of the extraneous wordage which serves more to confuse a student of pediatrics. The new edition grows larger and revision has been complete as the sections on therapy keep abreast of the advances made in the past two years.

Some of the new or rewritten discussions include: growth and development, congenital malformations, parenteral fluid therapy, congenital heart disease, infection, immunity and allergy in relation to pediatrics, inborn errors of metabolism, etc. There are 120 valuable tables covering differential diagnosis, drug selections, feeding schedules, food summaries, clinical manifestations, prescriptions, etc. The balanced presentation of the material makes it readable, practical—just what you want in a pediatric book.